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Original Report

Lung Scintigraphy and Helical Computed Tomography for the Diagnosis of Pulmonary Embolism: A Meta-Analysis

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Summary: To assess the diagnostic value of lung scintigraphy and helical computed tomography (hCT) in patients with suspected pulmonary embolism (PE), all English-language articles that described lung scintigraphy and hCT in patients with suspected PE were retrieved. Articles were assessed for strength of methodology, based on nine a priori-defined criteria. Parameters of diagnostic accuracy and results of management studies were calculated and evaluated. Lung scintigraphy is diagnostic in approximately 50% of patients with suspected PE. A normal perfusion scan has a chance of recurrent PE in two of 693 patients (0.3%; 95% CI: 0.2–0.4%; fatal in 0.15%). A high-probability lung scan is correlated with angiographically proven PE in 308 of 350 patients (88%; 95% CI: 84–91%). Pulmonary embolism was proven in 385 of 1529 patients (25%; 95% CI: 24–28%) with a nondiagnostic lung scan. Helical CT

studies were compared with angiography and lung scintigraphy in 1171 patients, with a prevalence of PE of 39%. The sensitivity and specificity of hCT was 283/320 (88%; 95% CI: 83–91%) and 374/408 (92%; 95% CI: 89–94%), respectively. Only one prospective management study using hCT was available. In patients in whom anticoagulants were withheld based on a normal hCT study, recurrent thromboembolic events occurred in six of 109 patients (5.5%; 95% CI: 2–12%), with one fatality (1%; 95% CI: 0.02–4.3%). Lung scintigraphy is evaluated extensively and yields a diagnostic result in 50% of patients. Helical CT has similar positive predictive value to a high-probability lung scan. However, the exact role of hCT in the management of patients with suspected PE needs to be determined in prospective studies. **Key Words:** Helical computed tomography—Lung scintigraphy—Pulmonary embolism.

In spite of improved prophylaxis, pulmonary embolism (PE) remains one of the main causes of morbidity and mortality in the western world. Approximately two to three patients per 1000 inhabitants are yearly suspected of having PE (1–3). Adequate diagnostic tests are required to distinguish patients who have PE from those that have other, often nonserious, illnesses. The reason for this diagnostic process are two-fold: the natural history of PE (i.e., missing the diagnosis) is thought to result in fatal and nonfatal recurrent PE in 30% of patients in each category, respectively (4). On the other hand, treatment with anticoagulants will result in bleeding complications, which are fatal and major in 1% and 7% per treatment year, respectively (5,6). Thus, both underdiagnosis and overtreatment should be avoided.

The diagnosis traditionally depended on clinical assessment. However, as demonstrated by studies that ap-

plied pulmonary angiography, the prevalence of pulmonary embolism in patients who are clinically suspected is only 30% (7–11). Furthermore, many patients are not diagnosed until they are seen by a pathologist (1). Hence, the threshold for suspicion is generally low, in order to miss as few patients as possible.

Although several noninvasive, diagnostic tests have been advocated over recent years, this overview is limited to the assessment of the evidence for the use of two diagnostic tests: lung scintigraphy (both perfusion and ventilation) and the newer helical computed tomography (hCT).

MATERIALS AND METHODS

Articles were identified through the Medline database and Current Contents, which described studies using lung scintigraphy and hCT in patients with suspected pulmonary embolism. The search was limited to articles

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published in the English language, with a final inclusion date of June 1, 1999. Abstracts were not included in the analysis.

Articles were reviewed and predefined criteria were set. Two types of publications were accepted in this analysis: diagnostic accuracy studies and management studies with follow-up. Several criteria, which were defined *a priori*, needed to be met for inclusion into this analysis. These were: 1) prospective study in consecutive patients; 2) adequate description of studied patients; 3) sensitivity and specificity evaluation versus pulmonary angiography; 4) blinded comparison with pulmonary angiography; 5) description of imaging techniques; 6) management studies with an adequate description of how follow-up was performed; 7) minimum follow-up of 3 months; 8) description of diagnosis in patients with recurrent symptoms; and 9) original (nonduplicated) articles only.

Using these criteria, the two diagnostic imaging modalities were assessed for diagnostic accuracy (i.e., sensitivity and specificity) and influence of different observer (inter-observer variability). Finally, the evidence of clinical utility in clinical practice, as demonstrated by management studies, was evaluated.

Statistical analysis was performed by means of a primary assessment of sensitivity, specificity when comparison was made with pulmonary angiography and recurrent thromboembolic events in management studies. Recurrent thromboembolic events were further subdivided into fatal PE and nonfatal PE. Overall 95% confidence intervals were calculated.

RESULTS

Lung scintigraphy

Technique

Lung scintigraphy uses radioactive tracers to assess basic lung physiology. Perfusion lung scintigraphy makes use of ^{99m}Tc -labelled macro-aggregates of albumin (12). These particles are injected intravenously with the patient supine and taking a deep breath, which guarantees optimal dispersion into the pulmonary vascular bed, where they become trapped. Only a fraction of the capillaries (in the order of 1%) are temporarily obstructed (13). The lungs are imaged in six standard projections using a gamma camera. Perfusion defects are identified as areas of hypo- or nonperfusion.

Ventilation scintigraphy is performed by introducing a radiotracer into the airways. This radiotracer may be a gas, such as ^{81m}Kr -Krypton or ^{133}Xe -Xenon, or an aerosol that is labelled with ^{99m}Tc , such as diethylene triamine penta-acetic acid (DTPA) or carbon (Technegas). These agents have different characteristics (14). The inert ^{81m}Kr gas has the advantage of a short half-life and may be used simultaneously with the perfusion scan,

but its costs and availability are limiting factors. ^{99m}Tc -labelled aerosols are easier to obtain, but have the disadvantage of central deposition, which is especially marked in patients with pulmonary diseases, resulting in diminished visualisation of the peripheral airways. Another inert gas, ^{133}Xe , is commonly used, but has the disadvantage that ventilation images have to be obtained before perfusion scintigraphy. The lungs are imaged in the same six projections as the perfusion lung scan. Complications of lung scintigraphy are rare and mainly caused by allergic reactions related to the administration of the albumin particles.

Classification

The classification of lung scan results have been a matter of debate for many years. Several attempts were made (11,15,16), and one study compared three classifications in a group of 96 patients (17). This study showed that the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria best predicted the presence of PE, but was worst in excluding the disease as compared with the other two classifications. Subsequently, the PIOPED criteria were revised in an attempt to improve the exclusion capability, but this led to a false-negative rate of up to 16% in patients with a low-probability lung scan (18).

A more clinically useful classification is to divide the lung scan results into three categories: 1) a normal perfusion scan, indicating the absence of pulmonary embolism; 2) a high-probability lung scan, defined as one or more defects of at least segmental size with normal matching ventilation, which indicates the presence of emboli; and 3) the remaining lung scan results, referred to as nondiagnostic scan, which would require further diagnostic tests (19). In a recent, direct comparison in 570 patients using this simple classification versus the revised PIOPED criteria, it was shown that the more complicated PIOPED criteria offer no advantage (20).

Using a variety of classifications, there is about 10 to 20% observer disagreement for lung scan reporting (21,22). The use of an anatomical lung segment chart is useful, because it improves the intra- and interobserver variability of reporting (23).

Normal lung scan

The clinical validity of a normal perfusion lung scan has been documented in three well-designed studies (24–26). In a total of 693 patients with a normal perfusion lung scan in whom anticoagulants were withheld, two patients (0.3%; 95% CI: 0.2–0.4%) had a thromboembolic event during a follow-up period of at least 3 months, one of them fatal. Hence, it is deemed safe to withhold anticoagulants in patients with a normal perfusion lung scan. An exception is the patient with a high clinical suspicion of pulmonary embolism and a normal perfusion lung scan (27).

High-probability lung scan

A total of nine studies were identified, which compared a high-probability lung scan (as defined by at least one segmental mismatch) with pulmonary angiography (8–11,16,28–31). The positive predictive value in 350 patients was 88% (95% CI: 84–91%). In the majority of patients, this is sufficient to warrant treatment with anticoagulants. However, one has to remain aware that other disorders than pulmonary embolism can cause perfusion–ventilation mismatch (32). Therefore, in patients who have an increased bleeding risk, it may be necessary to perform pulmonary angiography after all.

Nondiagnostic lung scan

Using a three-result classification, a total of 12 studies were identified that compared a nondiagnostic lung scan with pulmonary angiography (8–11,16,33–35). Pulmonary emboli were demonstrated in 385 of 1529 patients (25%; 95% CI: 24–28%). Therefore, a nondiagnostic lung scan result can suggest one management decision only: further diagnostic tests are required.

Helical computed tomography

Technique

The technique of helical (or spiral) CT first was applied for the diagnosis of pulmonary embolism in patients by Remy-Jardin et al. in 1992 (36). Briefly, helical computed tomography (hCT) is using radiograms similar to conventional CT, but hCT moves the patient through the scanner during imaging. This results in a helical motion of the radiograph tube around the patient. During scanning, intravenous contrast material is injected with an aim to opacify the pulmonary arterial tree. The obtained (volumetric) data can be reconstructed in transverse and multiplanar fashion.

Classification

Similar to pulmonary angiography, pulmonary emboli seen during hCT are defined as intraluminal filling defects or complete nonfilling of a pulmonary arterial branch (36). Although many different patterns of additional signs have been described, these have not been shown helpful in identifying patients with or without PE (37,38).

The interobserver variation has been investigated in several studies (39–41). The observer agreement, as shown by κ statistic, was high in all studies. However, more disagreement consisted in patients with previous nondiagnostic lung scans and in smaller pulmonary emboli, raising the issue of sensitivity in subsegmental PE (39,41). The sensitivity in this subgroup dropped from approximately 90 to 67% (39). This is an important issue, as up to 30% of patients with suspected PE will have emboli limited to the subsegmental arteries (42–44).

Diagnostic accuracy studies

Initial studies assessed the accuracy of helical CT in patients with (suspected) massive or central PE. The first study by Remy-Jardin in a selected series of 18 patients with central PE showed a sensitivity and specificity of 100% (36). Subsequently, a total of 12 studies assessed sensitivity and specificity using lung scintigraphy (45), pulmonary angiography (46–51) or a combination of lung scintigraphy and pulmonary angiography (39,40,52–54) as reference method. These studies are summarized in Table 1. The overall sensitivity and specificity are 88% (95% CI: 83–91%) and 92% (95% CI: 89–94%), respectively.

The high prevalence in some of these studies indicates that they were more focused on central PE, which may influence the overall figures. Several studies evaluated

TABLE 1. Summary of studies assessing the sensitivity and specificity of spiral computed tomographic (CT) angiography for the diagnosis of pulmonary embolism (PE)

Study	Reference method	n	Prevalence PE, %	Sensitivity	Specificity
Dresel et al. (45)	Lung scintigraphy	25	88	18/22	2/3
Blum et al. (46)	Angiography	10	70	7/7	3/3
Steiner et al. (47)	Angiography	38	79	30/30	8/8
Goodman et al. (48)	Angiography	20	55	7/11	8/9
Drucker et al. (49)	Angiography	40	33	9/15	26/32
Remy Jardin et al. (50)	Angiography	75	57	39/43	25/32
Garg et al. (51)*	Angiography	54	24	5/8	18/20
Van Rossum et al. (52)†	Scintigraphy/angiography	249	51	37/41	34/36
Van Rossum et al. (39)‡	Scintigraphy/angiography	149	46	64/68	78/81
Mayo et al. (40)	Scintigraphy/angiography	139	33	40/45	88/90
Pruszczyk et al. (53)	Scintigraphy/angiography	49	82	36/40	9/9
Kim et al. (54)	Scintigraphy/ultrasonography/angiography	110	23	23/25	75/85
Overall		1,171	39%	283/320 88%	374/408 92%

* Angiography in 26 patients; follow-up in 28 patients. †CT only in 77 patients with non-normal perfusion scintigraphy; angiography in 42 patients with non-diagnostic lung scan and in 3 patients with high probability lung scan and normal spiral CT. ‡CT in all 149 patients: PE excluded by perfusion scan (40) or angiogram (41); PE proven by high probability scan (53) or angiogram (15).

the influence of embolus size on sensitivity and specificity (39,48,49). This revealed that the sensitivity is markedly lower for subsegmental PE, and appears to be in the range of 50 to 65% (39,48,49).

Another important issue is the number of technically inadequate helical CT investigations. This ranged between 3 and 6% (40,51,52,54). More recent studies have shown that these figures can be improved further. Using smaller collimation of 2 mm (55) and multiplanar reconstruction algorithms (56) can further improve visualization of segmental and even subsegmental arteries. Thus, the current accuracy figures may be further improved on with the implementation of better imaging protocols.

Management studies

Only a few studies have evaluated the outcome of patients with suspected pulmonary embolism in which helical CT played a role in management. One prospective management study in 164 patients with nondiagnostic lung scan findings and normal duplex ultrasonography of the leg veins made use of hCT (57). This study showed PE in 39 (24%) patients, who were promptly treated with anticoagulant therapy. Angiography was performed in 15 patients with normal hCT findings caused by high clinical suspicion, and this showed PE in one patient. Three months follow-up was obtained in the 109 patients with a normal hCT study, who did not receive anticoagulant therapy based on a normal hCT study. One patient died because of recurrent PE, two developed nonfatal recurrent PE, and three were diagnosed with unexplained deep-vein thrombosis (one further patient suffered local thrombosis following angiography). Thus, recurrent thromboembolic events occurred in 5.5% of patients (95% CI: 2–12%), with a 1% fatality rate (95% CI: 0.02–4.3%). These results compare unfavorably with those of management studies, which used lung scintigraphy and pulmonary angiography (58–60).

A second study consisted of a retrospective review of 126 patients who had hCT during the course of their management (61). Six months follow-up was complete in 78 patients with a normal hCT who remained untreated. None of these patients died of recurrent PE, and autopsy revealed small PE in only one patient. For comparison, a group of 46 patients with normal perfusion scintigraphy showed no recurrent PE, but in a group of 132 patients with low probability two fatal and one nonfatal embolic events were recorded.

Finally, another retrospective review of 143 patients who underwent hCT for suspected PE was carried out (62). Six months follow-up was aimed for in 113 patients with normal hCT patients who remained untreated. During follow-up, contact with 13 patients was lost and 19 died (none reportedly from PE), whereas no recurrent PE was documented in the remaining 81 patients.

DISCUSSION

Lung scintigraphy has been well evaluated. For patient management, two results are sufficient: a normal perfusion scan adequately excludes PE, whereas a high-probability scan result is sufficient proof to warrant anticoagulant therapy in most patients. Nevertheless, one needs to be aware that PE may be absent in as many as 12% of patients with a high-probability lung scan result. Helical CT is a newer technique that has not been fully evaluated yet. The results are promising, and there is some evidence that hCT can replace (in part) lung scintigraphy. If thrombus is evident at hCT, this is sufficient to warrant anticoagulant therapy. In patients with suspected PE and normal hCT findings, however, further diagnostic work-up is required. Some have suggested that alternative findings during hCT, such as atelectasis, tumor, or pleural effusion in the absence of PE may adequately exclude PE and that patients could remain without anticoagulant therapy. However, a recent study suggested that alternative findings are equally present in those with and without PE (38). Furthermore, no prospective management studies exist to support this notion. Thus, at present, it should be regarded unsafe to withhold anticoagulant therapy in patients with normal hCT findings.

What could be the role of hCT in the future? Although the exact role of hCT has not been fully established, it is expected that it will play a significant role in the future management of patients with suspected PE. This is not only because of its diagnostic accuracy, but also because of its noninvasive nature and the wide availability. A diagnostic strategy using hCT should try to increase the prevalence of PE in patients before referral for hCT. A combination with plasma D-dimer testing and venous ultrasonography seems a good way forward, as recently demonstrated in a large management study (63). In this study, 47% of patients either had PE excluded by D-dimer of proven by ultrasonography. In the remaining 53% of patients, the prevalence of PE was 25%. At this point in the management strategy, one could either perform perfusion lung scintigraphy (with 8% of patients normal), leaving 39% of patients for hCT (with a prevalence of PE of 33%). Alternatively, one could perform hCT in all 53% of patients and leave out lung scintigraphy altogether. Finally, clinical probability should be taken into consideration if hCT does not show PE. If the clinical probability is low, one could withhold anticoagulant therapy, whereas pulmonary angiography would be required in the 5–10% of patients with a normal hCT and a high clinical probability of PE. It should be reiterated, that hCT should not be used in routine management of patients with suspected PE until the results of ongoing (and future) prospective management studies show its safety and utility.

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